29 (New). A method of modulating cellular processes modulated/mediated by RIP directly or indirectly, comprising causing one or more polypeptide according to claim 13, capable of binding to RIP, to come into contact with the interior of said cells.

REMARKS

The present communication is responsive to the official action of July 16, 2002. Claims 13-16, 18, 19, and 27-29 presently appear in this case. Claims 18, 19, 27 and 28 have been withdrawn from consideration. Claims 13, 15 and 16 have been rejected. Claim 14 has been objected to, but has been indicated to be allowable if rewritten in independent form. The official action of July 16, 2002, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

It is noted that the examiner has reconsidered and retained the restriction requirement, stating that the proteins and antibodies are unrelated as they differ in their structure and physical chemical properties and that they are, therefore, patentably distinct. It is noted that the examiner has not commented on applicants' arguments that the antibody would be obvious from the protein and that maintaining this restriction requirement and issuance of the antibody claims in a divisional application would result in two patents with

claims that are not patentably distinct, which is clearly forbidden by the MPEP. This restriction requirement is again respectfully traversed.

It is respectfully requested that the examiner explain why he does not consider this case to be on all fours with *In re Gold*, 42 USPQ2d 1095 (Comm'r Pats 1996), a copy of the slip opinion of which was attached to applicants' amendment of May 6, 2002. Further, the examiner is asked to explain why MPEP §803, quoted and discussed in applicants' last response, is distinguishable from the present situation. The Office has a policy that no restriction requirement be made which might result in issuance of two patents for the same invention. It is believed that this policy is controlling here. Accordingly, antibody claims 18, 19 and 28 should be examined with the elected polypeptide claims. Once polypeptide claims are found to be allowable, method of use claims 20, 27 and 29 should also be examined in this case. Note that claim 26 was inadvertently abandoned in the previous response and the subject matter thereof has now been reinserted herein as new claim 29. Thus, aside from the claims as originally grouped in Groups III, IV and V of the restriction requirement, all of the non-elected claims have now been deleted. Reconsideration and withdrawal of this

restriction requirement and examination of all of the claims in this case are, therefore, respectfully urged.

Claims 13, 15 and 16 have been rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an RIP-associated protein (RAP) encoded by a DNA sequence in a deposited clone, does not reasonably provide enablement for any fragment thereof which is capable of binding to RIP, any analog thereof which is capable of binding to RIP, any polypeptide which "has" the amino acid sequence of a fragment of RIP, or any pharmaceutical composition using any of such compounds for treating any disease. The examiner states that applicants have disclosed only one polypeptide which has the required activity, and this does not support the breadth of the claims. This rejection is respectfully traversed.

The enablement requirement of 35 U.S.C. §112 is discussed at section 2164 *et seq* of the MPEP. MPEP §2164.01 states that any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The question is whether the experimentation needed to practice the invention is undue

or unreasonable. If the invention can be practiced without undue or unreasonable experimentation, the enablement requirement is considered to be met. The undue experimentation factors of *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) are set forth at MPEP §2164.01(a). These factors include:

(a) the breadth of the claims;

(b) the nature of the invention;

(c) the state of the prior art;

(d) the level of one of ordinary skill;

(e) the level of predictability in the art;

(f) the amount of direction provided by the inventor;

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the examiner takes the position that the scope of the claims is broader than the enabled disclosure with respect to fragments of the disclosed polypeptide sequences and with respect to analogs thereof.

With respect to the breadth of the claims, claim 13, in part (a), is directed to a specific polypeptide, which the examiner concedes is sufficiently enabled (see the allowability of claim 14). Part (c) includes analogs thereof

having no more than ten substitutions, deletions or additions of amino acid residues. Claim 13 has now been amended to clarify the language about the ten amino acid changes to make it absolutely clear that any such analog has no more than a total of ten amino acid residues which differ from the base sequence. Thus, part (c) now specifies that the analogs have no more than ten changes in the amino acid sequence with each such change being a substitution, deletion or insertion of a single amino acid. It further specifies that the analog must bind to RIP. It should be noted that the amino acid sequence of SEQ ID NO:2 has 522 residues. Thus, ten changes in the 522 residue sequence amounts to only about 1.9%, i.e., the claimed analogs have a minimum of greater than 98% identity to the specified sequence.

The examiner's attention is invited to the Revised Interim Written Description Guidelines Training Materials, which have been published by the Patent and Trademark Office, Example 14 "Product by Function". There, a claim to a specific sequence and variants thereof that are at least 95% identical thereto and have a specified function was held to comply with the written description requirement. The Guidelines state:

> The single species disclosed is representative of the genus because all members have at least 95% structural identity with the referenced compound and

> because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

While these Training Materials relate to written description, rather than enablement, they should be instructive also from the standpoint of enablement to the extent that the Patent and Trademark Office has conceded that, with a claim such as the present, a single example is representative of the entire genus of variants with 95% identity. Thus, this is not a particularly wide breadth for an analog claim.

While claim 13 is somewhat broader than the specific sequence of (a), the claimed scope is necessary in order to reasonably cover the invention. In MPEP §2164.08, relating to enablement commensurate in scope with the claims, the MPEP quotes the following from *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

It should be noted that the definitions of fragment, analog and derivative at claim 13(b), (c) and (d), respectively, all require that the fragment have the ability to bind to RIP. The polypeptides have utility merely by binding, for example in affinity chromatography, and, therefore, it is not absolutely necessary to assay for intracellular activity. In view of the stated activity and the direction in the specification, which will be discussed below, and the reasonable breadth of the analogs, the breadth is not unduly broad and the experimentation to find everything within the scope of these claims would not be undue.

The nature of the present invention is such that substantial experimentation is reasonably conducted by those of ordinary skill in the art. The present claims are directed to recombinantly-produced polypeptides. Applicants concede that there is not 100% predictability in this field. However, this does not mean that an applicant must be limited to exemplified embodiments. As long as it is shown that the experimentation to determine what falls within the claim is not undue, the enablement requirement is met. As discussed below, the experimentation is not undue.

As to the state of the prior art, there is no close prior art. The reference cited by the examiner here is not prior art for the reasons which will be explained below with

respect to the art rejection. Thus, there is no prior art reason for limiting the scope of the claims. Furthermore, a review of prior patents will show that it is common for those of ordinary skill in the art to take part in this degree of experimentation as there are scores of patents that include claims with novel proteins and analogs thereof with 95% or even less identity. This is not a case of first impression.

As to the level of one of ordinary skill, inventions involving biotechnology involve a very high level of ordinary skill. Because of this extremely high level of ordinary skill, even complex experimentation is not necessarily undue or unreasonable.

The next two *Wands* factors, the level of the predictability in the art and the amount of direction provided by the inventor, go hand in hand. As to the predictability in the art, when changing the sequence by less than 2%, there would be an expectation that the function is maintained. Thus, it is reasonably predictable that such a small number of random changes will work, but in any event, it is readily testable in order to determine which will have the claimed function and which will not have the claimed function. The present claim always requires that the result of the amino acid changes have the ability to bind to RIP, i.e., by

definition, the activity must be retained. The present specification states in paragraph 89:

> While any technique can be used to find potentially biologically active proteins which substantially correspond to RAP proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications. The proteins expressed by such clones can then be screened for their ability to bind to various RIP and to modulate RIP activity in modulation/mediation activity of the intracellular pathways noted above.

See also paragraph 97, where it states:

> When the exact effect of the substitution or deletion is to be confirmed, one skilled in the art will appreciate that the effect of the substitution(s), deletion(s), etc., will be evaluated by routine binding and cell death assays. Screening using such a standard test does not involve undue experimentation.

Furthermore, substantial guidance is provided in the present specification as to preferred substitutions which would be expected to retain the activity of the base compounds, i.e., the RAP protein. Note, for example, paragraphs 90-97. Those of ordinary skill in the art are aware that binding assays are relatively simple tests. Whole libraries can be screened at one time with the yeast two-hybrid assay described in the Example beginning at paragraph 170 of the present specification. Other binding assays using microarray technology are well known in the art and can test thousands of

compounds at once for binding. This is not undue experimentation in this art, particularly in view of the small number of amino acids that may be changed in accordance with the language of the claims. Accordingly, it is apparent that there is substantial direction provided in the specification about how to do these standard binding assays. This is all that is necessary to do in order to determine whether any given analog having no more than ten amino acid changes has the ability to bind RIP. These minor changes are not unreasonable. Accordingly, substantial direction is provided by the specification.

As far as working examples are concerned, as discussed above, a working example of the yeast two-hybrid binding assay is given in the specification. While there are no working examples given in the specification for analogs, fragments and derivatives, the guidance of the specification explains how to determine whether any given compound falls within the scope of the claims, and therefore additional working examples are not necessary.

Finally, the last *Wands* factor is the quantity of experimentation needed to make or use the invention based on the content of the disclosure. It is true that substantial experimentation will be necessary. However, as stated at MPEP §2164.06, the test is not merely quantitative since a

considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are not the controlling factors. Procedures for making variants of the RAP protein which have at least 98% identity with the sequence thereof are conventional in the art, such as the technique detailed in paragraphs 99-106 of the present specification.

The assays involved to determine whether any such analog has the ability to bind RIP are routine, as is disclosed in the specification and discussed above. All of the claimed analogs must possess the specified activity of being able to bind RIP. There is a reduction to practice of the disclosed species of RAP protein. The fact that any single amino acid change might have a profound effect or no effect, is not really dispositive. Here, standard binding assays are known and so any given analog can readily be tested without undue experimentation. Indeed, whole libraries of analogs can be tested simultaneously. Thus, applicants need not rely upon predictability of analogs with respect to changes (even though there is reasonable predictability with analogs of greater than 98% identity), but are relying on testing in the standard assays described in the specification

and discussed above, which can be carried out in large numbers at the same time.

The level of skill in the art is high and the assays are standard and can be conducted with many different analog sequences at the same time. Thus, while substantial experimentation may be needed to establish all of the sequences of which fall within the scope of the claim, i.e., meet the functional requirement of binding to RIP, such experimentation is not undue or unreasonable. Indeed, for any given sequence, the testing is virtually negligible in order to test for binding to RIP.

The same is true with respect to fragments. Fragments can be made by removing one amino acid at a time from either end and testing for binding activity using the standard assays described in the specification and discussed above. Once the activity is lost, it would not be expected that smaller fragments would be operable. Thus, the amount of experimentation needed to find fragments is even less than that needed to find analogs.

With respect to derivatives, there is no reason to even predict that derivatizing an amino acid of a sequence will cause this sequence to lose its activity. Derivatives are defined in the present specification at paragraphs 108-110, and are explicitly defined so as to include only those

derivatives that do not change one amino acid to another of the 20 commonly-occurring natural amino acids. This is now specified in the claims. Thus, derivatives are not analogs. They are simply standard modifications of the side groups of one or more amino acid residues, or the residues on the N- or C-terminal residues. There is no more reason that these would cause the sequence to lose its activity than for a salt. In any event, the claim requires that the activity be retained, and, if necessary, the standard binding assays discussed above can be used on the derivatives to confirm that no activity is lost. Thus, it would certainly not involve undue experimentation in order to establish that such functional derivatives have the required claimed properties.

For all of these reasons, the enablement requirement is fulfilled with respect to the full scope of claim 13.

With respect to claim 15, the word "has" has now been amended to read "comprises" as in claim 13. Thus, this claim satisfies the enablement requirement for the reason as discussed above with respect to paragraph (b) of claim 13.

With respect to claim 16, this claim has now been amended so as no longer to read on a pharmaceutical composition for the modulation of the RIP effect on cells, but merely to broadly call for a composition comprising the peptide according to claim 13 and a pharmaceutically

acceptable carrier, as is supported in paragraph 164 of the present specification. Thus, the examiner's comments with respect to claim 16 are no longer applicable to the claim as amended. For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 13, 15 and 16 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter for which the specification does not reasonably provide a written description. The examiner particularly refers to fragments, analogs, analogs of fragments, polypeptides which "have" the specified amino acid sequence, and pharmaceutical compositions for treating any disease. The examiner refers to the written description guidelines. This rejection is respectfully traversed.

As pointed out above, SEQ ID NO:2, which is encoded by the DNA of the deposited clone of claim 13(a), has 522 residues. The claims do not encompass more than ten amino changes therein, which amounts to only about 1.9%. Accordingly, the claimed analogs have a minimum of greater than 98% identity to the specified sequence.

The examiner's attention is respectfully drawn to the Revised Interim Written Description Guidelines Training Materials and, particularly, Example 14: "Product-by-Function". In that example, the specification exemplified a protein isolated from

liver that catalyzed the reaction of A→B, which isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplated, but did not exemplify, variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions, and additions. The specification indicated that procedures for making proteins with substitutions, deletions, insertions, and additions is routine in the art and provided an assay for detecting the catalytic activity of the protein.

This description in the specification is very similar to the description which appears in the present specification. The present specification exemplifies a RAP protein that binds RIP. The sequence of this protein is specified. The specification contemplates, but does not exemplify, variants of the protein wherein the variant can have substitutions, deletions, insertions, and additions. The present specification also indicates that procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art (see, for example, paragraphs 99-106) and provides an assay for determining whether any given protein binds to RIP. See also paragraph 97.

In Example 14 of the Training Materials, the claim is directed to:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B.

The present claim 13 is drawn to a method of use that includes an analog of RAP having at least 98% identity with the sequence of RAP and has the ability to bind to RIP. Thus, this claim is substantially identical in format to that of Example 14.

The analysis in the Training Materials acknowledges that procedures for making variants of SEQ ID NO:3 are conventional in the art and that an assay is described which will identify other proteins having the claimed functionality. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity were conceded as being conventional in the art. It would, of course, be understood that procedures for making variants of the polypeptide of paragraph (a) of claim 13, which have 98% identity to that sequence and retain its binding activity to RIP are also conventional in the art.

The analysis goes on to point out that all variants of the claim must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO:3. Furthermore, because of the "having" language, the protein claimed may be larger than SEQ ID NO:3 or its variant with 95% identity to SEQ ID NO:3. The analysis points out that the specification contains a reduction to practice of the single disclosed species. The analysis concludes:

> The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variations since all the variants must possess the

> specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> Conclusion: The disclosure meets the requirements of 35 USC §112, first paragraph, as providing adequate written description for the claimed invention.

Thus, it is apparent that if the single species disclosed is representative of the genus and an assay is present for identifying the members of the variants which are capable of the specified functionality, the written description requirement is met, regardless of the protein chemistry arguments made by the examiner. Here, the 98% identity is much higher than the 95% identity which was found to satisfy the written description guidelines in the training materials.

As to the "fragment" portion of the claim, it would be expected that if one amino acid were removed from the C-terminus that the fragment which remains will still be active. It is within the skill of the art to remove one amino acid at a time from either end of a protein or an analog, and then run the assay to determine if the fragment retains functionality. Once a

fragment loses functionality, then it is not necessary to test any further. This does not involve undue experimentation. Thus, because any such fragment must have a portion of the specified sequence and a simple assay is readily available, as is a rational means to determine which fragments would be expected to be operable, the full sequence, representing the single species of the RAP protein and its functional fragments, is representative of the genus. One of ordinary skill would thus conclude that applicants were in possession of the necessary common attributes possessed by the members of the genus. Therefore, the requirements of 35 U.S.C. §112, first paragraph, as to providing adequate written description for the claimed invention are met.

As to the examiner's comment that the claim language is open-ended, it is noted that the claim language in Example 14 of the training materials discussed above is also open-ended and was found to be acceptable. In this regard, see also paragraph 111 of the present specification.

As to the examiner's comments about analogs of fragments, claim 13(c) has now been amended to delete such reference.

As to claim 16, it is believed that the amendment to this claim obviates the examiner's comments about it.

Accordingly, reconsideration and withdrawal of the written description rejection are respectfully urged.

Claims 13, 15 and 16 have been rejected under 35 U.S.C. §102(e) as being anticipated by USP 6,232,081 of Harper et al. The examiner states that Harper teaches an isolated polypeptide which is a fragment of the claimed polypeptide of SEQ ID NO:2. The examiner states that the functional properties of the reference fragment are an inherent property thereof. This rejection is respectfully traversed.

The present application has an effective filing date at least as early as March 19, 1998, the date of filing of the parent PCT application. The Harper patent is based on an application filed October 15, 1998, which is a continuation-in-part of another application filed on October 16, 1997. Thus, the Harper patent is only available as a reference if it is entitled to the filing date of its parent application. As stated at MPEP §2136.03(IV), the filing date of a U.S. parent application can only be used as the 35 U.S.C. §102(e) date if it supports the claims of the issued child.

The four claims of the issued Harper child application are all directed to a method for the detection of one or more NF-κB regulatory factors. Attached hereto is a certified copy of the specification as filed of application no. 08/951,621, which was the parent application of Harper filed on October 16, 1997. By comparing the specification of the Harper patent with the specification of the parent

application, it can be seen that the paragraphs at column 5, lines 18-53; column 7, lines 7-23 (and Figures 8-12); column 31, lines 43-51; and column 40, line 64, through column 48, line 64, of the Harper patent are all new, and these portions do not appear in the parent application. The only support for the detection of NF-κB regulatory factors as claimed in the Harper patent is found in these new paragraphs. There is no support whatsoever for such claims in the parent application as filed, as can be seen by the attached certified copy.

Accordingly, the 102(e) date of Harper is October 15, 1998, and not October 16, 1997. Thus, it is not available as a reference against the present application which has an effective filing date at least as early as March 19, 1998. It is not necessary to determine whether the present application is entitled to the effective filing date of the Israeli priority date of March 19, 1997, in order to determine that Harper is not available as a reference. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the reference of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims

Claims 13, 15 and 16 have been amended as follows:

13 (Amended). An isolated polypeptide which is capable of binding to RIP and modulating or mediating the intracellular activity of RIP, which polypeptide ~~is~~comprises:

(a) a RIP-associated protein (RAP) encoded by a DNA sequence in a clone deposited with Collection Nationale de Cultures de Microorganismes under accession number I-2706;

(b) a fragment of (a) which ~~is capable of binding~~binds to RIP ~~or inhibiting the NF-κB inducing effect of RIP~~;

(c) an analog of (a) ~~or (b) which differs from the~~having no more than ten changes in the amino acid sequence of (a), each said change being a substitution, deletion or insertion ~~or (b) by no more than 10 substitutions, deletions and/or insertions~~ of an amino acid, ~~residues and is capable of binding~~which analog binds to RIP ~~or inhibiting the NF-κB inducing effect of RIP~~; or

(d) a derivative of (a), (b) or (c) by modification of a functional group which occurs as a side chain or an N- or C-terminal group of one or more amino acid residues thereof without changing one amino acid to another of the twenty

commonly-occurring natural amino acids, which derivative binds to RIP.

15 (Amended). A polypeptide according to claim 13, which ~~has~~ comprises the amino acid sequence of (b).

16 (Amended). A ~~pharmaceutical~~ composition ~~for the modulation of the RIP effect on cells,~~ comprising~~, as active ingredient,~~ the polypeptide according to claim 13, and a pharmaceutically acceptable carrier.

Claims 17 and 21-24 have been deleted.

Claim 29 has been added.